L11: Entry 9 of 37 File: USPT Jan 30, 2001

DOCUMENT-IDENTIFIER: US 6180082 B1
TITLE: Method to enhance tissue accumulation of radiolabeled compounds

BSPR:
Radiolabelled compounds are used for both tumor detection and tumor therapy. Many tumor cells have a higher density of cell receptors for various circulating compounds than do non-tumor cells; e.g., endocrine tumors show a high density of cell surface receptors for somatostatin, and brain gliomas show a high density of receptors for epidermal growth factor. Thus a radiolabeled compound that binds to these cellular receptors preferentially binds to the tumor cells. Additionally, angiogenesis, the formation of new blood vessels from established microvasculature, is a critical process for tumor growth. Primary tumors and metastases will not grow beyond 2 mm in diameter without an enhanced vascular supply. Angiogenic cells also have a higher density of cell receptors for various circulating compounds than do non-angiogenic vascular tissue; e.g., receptors for both somatostatin and vascular endothelial growth factor are higher in angiogenic tissue. Thus a tumor can also be detected by radiolabeled compounds binding to the angiogenic cells that are closely associated with the tumor cells.

BSPR:
An ideal tumor imaging agent would maximize the radioactivity at the target cells, and minimize the background signal, resulting in a well-defined image of the tumor foci. For example, .sup.111 In-DTPA-D-Phe-1-octreotide and .sup.123 I-vasoactive intestinal peptide, two receptor-based radioligands, have been used to localize primary endocrine tumors as well as metastatic liver lesions. See A. Kurtaran, et al., "Vasoactive Intestinal Peptide and Somatostatin Receptor Scintigraphy for Differential Diagnosis of Hepatic Carcinoid Metastasis," The Journal of Nuclear Medicine, vol. 38, pp. 880-881 (1997).

BSPR:
The recycling of the cellular receptors depends on the fate of the ligand-receptor complex. Many, if not most, peptide compounds (including peptide and protein hormones) that bind to surface receptors are internalized as a ligand-receptor complex by endocytosis, i.e., invagination of the plasma membrane. Examples of peptides that have been shown to be internalized as part of a ligand-receptor complex include nerve growth factor, fibroblast growth factor, epidermal growth factor, platelet-derived growth factor, cholecystokinin, vascular endothelial growth factor, vasoactive intestinal peptide, gastrin-releasing peptide, leukemia inhibitory factor, somatostatin, oxytocin, bombesin, calcitonin, arginine vasopressin, angiotensin II, atrial natriuretic peptide, insulin, glucagon, prolactin, growth hormone, gonadotropin, thyrotropin-releasing hormone, growth hormone-releasing hormone, gonadotropin-releasing hormone, corticotropin-releasing hormone, interleukins, interferons, transferrin, substance P, neuromedin, neurotensin, neuropeptide Y, and various opioids. This internalization takes time--minutes or even hours. See G. Morel, "Internalization and Nuclear Localization of Peptide Hormones," Biochemical Pharmacology, vol. 47(1), pp. 63-76 (1994); D. Nouel et al., "Differential Internalization of Somatostatin in COS-7 Cells Transfected with SST.sub.1 and SST.sub.2 Receptor Subtypes: A Confocal Microscopic Study Using Novel Fluorescent Somatostatin Derivatives," Endocrinology, vol. 138, pp. 296-306 (1997); L.-H. Wang et al., "Ligand Binding, Internalization,

Degradation and Regulation by Guanine Nucleotides of Bombesin Receptor Subtypes: A Comparative Study," Biochimica et Biophysica Acta, vol. 1175, pp. 232-242 (1993). Even monoclonal antibodies have been shown to be internalized into the cell. See O. W. Press et al., "Comparative Metabolism and Retention of Iodine-125, Yttrium-90, and Indium-111 Radioimmunoconjugates by Cancer Cells," Cancer Research, vol. 56, pp. 2123-29 (1996).

BSPR:
High densities of somatostatin receptors, especially somatostatin receptor subtype 2 (SST-2), have been found on cells from a wide variety of tumors, including endocrine tumors, melanomas, breast carcinomas, Merkel cell tumors, lymphomas, small cell lung carcinomas, gastrointestinal tumors, astrocytomas, gliomas, meningiomas, carcinoid tumors, islet cell tumors, renal cell carcinomas, neuroblastomas, and pheochromocytomas. See E. A. Woltering et al., "The Role of Radiolabeled Somatostatin Analogs in the Management of Cancer Patients," Principles & Practice of Oncology, Vol. 9, pp. 1-15 (1995); and E. A. Woltering et al., "Somatostatin Analogs: Angiogenesis Inhibitors with Novel Mechanisms of Action," Investigational New Drugs, vol. 15, pp. 77-86 (1997). The radiolabeled somatostatin analog .sup.111 In-Pentetreotide, known to bind SST-2 receptors on cell membranes, has been shown to bind to pituitary tumors, endocrine pancreatic tumors, carcinoids, paragangliomas, pheochromocytomas, medullary thyroid carcinomas, small-cell-lung cancers, neuroblastomas, meningiomas, breast carcinomas, renal cell carcinomas, gliomas, astrocytomas, melanomas, and lymphomas. .sup.111 In-Pentetreotide has also been used to treat metastatic glucagonoma and carcinoid tumors. See Wiseman et al., 1995; Krenning et al., "Radiotherapy with a radiolabelled somatostatin analogue, [.sup.111 In-DTPA-D-Phe1]-octreotide. A Case History," Annals of the New York Academy of Sciences, vol. 733, pp. 496-506 (1996); and M. Fjalling et al., "Systemic radionuclide therapy using indium-111-DTPA-D-Phe-1-octreotide in midgut carcinoid syndrome," Journal of Nuclear Medicine, vol. 37, pp. 1519-21 (1996).

BSPR:
U.S. Pat. No. 5,597,894 discloses using multi-tyrosinated somatostatin analogs given by bolus injection or short infusion (up to 60 min) to diagnose and treat tumors with peptide-specific surface receptors.

DEPR:
Suitable radioisotopes include radioisotopes that emit alpha, beta, or gamma radiation, preferably gamma radiation which is easier to image using current technology. Examples are radioisotopes derived from Gallium, Indium, Technetium, Yttrium, Ytterbium, Rhenium, Platinum, Thallium, and Astatine, e.g., .sup.67 Ga, .sup.111 In, .sup.99m Tc, .sup.90 Y, .sup.86 Y, .sup.169 Yb, .sup.188 Re, .sup.195m Pt, .sup.201 Ti, .sup.211 At. Radioisotopes suitable for therapeutic treatment include Auger-electron-emitting radioisotopes, e.g. .sup.125 I, .sup.123 I, .sup.124 I, .sup.129 I, .sup.131 I, .sup.111 In, .sup.77 Br, and other radiolabeled halogens. The choice of a suitable radioisotope depends on a variety of factors including the type of radiation emitted, the emission energies, the distance over which energy is deposited, and the physical half-life of the radioisotope. Preferred radioisotopes are those having a radioactive half-life corresponding to, or longer than, the biological half-life of the receptor-dependent compound. Preferably the radioisotope has a half-life between about 1 hour and 60 days, preferably between 5 hours and 60 days, more preferably between 12 hours and 60 days. .sup.125 I has an advantage over other emitters that produce high-energy gammna rays (i.e., .sup.111 In and .sup.113 I) which require inpatient hospitalization and isolation. .sup.125 I will allow the development of outpatient-based treatments due to the limited amounts of radiation that escapes the body.

DEPR:
The amount of radiolabeled compound to be administered in radiotherapy is determined by the specific condition to be treated, the radiolabeled compound used, and patient-dependent variables, including size, weight, receptor density in the target cells, and the severity of disease. The efficacy of the

therapy can be assessed by monitoring techniques well known in the art, including radioimaging and monitoring as described above.

DEPR:
In each of five successive months, a bolus injection of about 180 mCi of .sup.111 In-pentetreotide (OctreoScan.RTM., Mallinckrodt Medical, Inc., St. Louis, Mo.) was given. The external gamma dose rates from radioligand accumulation in the neck tumor area were measured immediately and 24 hr after injection. After the treatment of the fifth month, the patient was monitored for radioligand uptake for an extended period--at 2, 4, and 8 days after the injection. These data are shown below in Table 1 and are also presented in FIG. 1 as the lower curve labeled "Bolus Dose."

DEPR:
Triplicate T-75 flasks containing IMR-32 and SKNSH cells which had been incubated overnight with .sup.111 In-pentetreotide as in Example 2 were used for DNA extraction. Cells were removed from the culture surface using a sterile rubber policeman. The suspended cells were washed three times in cold Dulbecco's phosphate buffered saline and processed through a DNA extraction procedure according to the vendor's directions (GenomicPrep.RTM. cells and Tissue DNA Isolation Kit, Pharmacia Biotech, Piscataway, N.J.). The cells were incubated in the Cell Lysis Solution of the DNA isolation kit at 37.degree. C. for 10 minutes. Next, 3 .mu.l of the Rnase Solution was added to the cell lysate, followed by thorough mixing and incubation at 37.degree. C. for 1 hour. The samples were cooled to room temperature, and 200 .mu.l of the Protein Precipitation Solution were added. Following vortexing, the contents of each tube were centrifuged at 14,000.times.g for 1 min, and the DNA pellet was washed with 70% ethanol. Following drying the DNA was hydrated in a DNA Hydration Solution, and the concentration of DNA determined by spectrometry at 260 nm. One hundred microgram (100 .mu.g) quantities of each treatment were transferred to radioactive counting vials, and the amount of radioactivity associated with each was measured in a Beckman 5500 gamma counter. The data, as presented in Table 6, were obtained as counts per minute (cpm). The differences between radioactivity measured in cells incubated solely with radioligand and in cells incubated with both radioligand and unlabeled ligand were statistically analyzed using ANOVA. The rate of accumulation of .sup.111 In-pentetreotide on DNA of IMR-32 cells is shown in FIG. 12.

DEPR:
Additionally, the DNA from each flask was divided in half, and 1 mg of DNA from each flask was treated with proteinase-K (Lite Technologies, Gaithersburg, Md.) for 1 hour at 37.degree. C. The enzyme-treated DNA was then reprecipitated with ethanol and sodium acetate, washed with cold ethanol, and redissolved in DNA hydration solution. The concentration was determined by spectrophotometry at 260 nm. One hundred microgram (100 .mu.g) of protease-treated DNA and an equal quantity of untreated DNA were transferred to radioactive counting vials and the amount of radioactivity measured in a Beckman 5500 gamma counter, as described above. The data, as presented in Table 7 and FIG. 13, were obtained as counts per minute (cpm).

DEPR:
Surprisingly, the .sup.111 In-pentetreotide bound to the DNA of IMR-32 cells was resistant to the effects of the nonspecific proteinase-K. Overall, the protease treatment removed only 10-13% of total bound CPM, showing that the association of the radioligand with DNA was not due to binding to nonspecific proteins such as histones.

DEPR:
Following short-term drug exposure, the effect of each dose of .sup.125 I-WOC-4a on viability of IMR-32 and PANC-1 cells was determined. Mean cell viability (.+-.SD) was calculated and the dose effect analyzed by analysis of variance (ANOVA). Student's t-tests were used when viability was compared for a single drug concentration between the two cell types. In the long-term exposure group, mean cell viability (.+-.SD) was calculated for each treatment group and compared to those of the control group by ANOVA ($p<0.05$).

DEPR:
When IMR-32 cells were incubated for 48 hr with .sup.125 I-WOC-4a at doses ranging from 0.1-100 CPM/cell, there was a dose-dependent decrease in cell viability, as measured by the MTT assay. .sup.125 I-WOC-4a induced a 33% decrease in cell viability at a dose of 1 CPM/cell and an 87% decrease in cell viability at a dose of 100 CPM/cell (FIG. 14). These differences were statistically different by ANOVA ($p<0.05$). However, when the SST-2 negative cell line (PANC-1) was exposed to the same concentrations of .sup.125 I-WOC-4a, no statistically significant difference in cell viability between control and any treatment group (n=21 per group) was found as shown in FIG. 14. These results indicate that following a short-term (48hr) exposure, .sup.125 I-WOC-4a induces SST-2-dependent cytotoxicity.

DEPR:
For evaluating the effect of a long-term (4-week) exposure to .sup.125 1I-WOC-4a on SST-2 expressing cells, IMR-32 cells were exposed to either 1 CPM/cell .sup.125 I-WOC-4a, 1 CPM/cell .sup.125 I-WOC-4a with 10.sup.6 M octreotide acetate, 10.sup.6 M octreotide acetate alone, .sup.125 I alone, or .sup.125 I with octreotide acetate. Cell viability of each treatment group was compared to control values after a four-week, cryopreserved exposure. These data are shown in FIG. 15. .sup.125 I-WOC-4a induced statistically significant cytotoxicity; however, no cytotoxicity was seen following exposure to similar doses of .sup.125 I alone or .sup.125 I with octreotide acetate. In addition, .sup.125 I-WOC-4a cytotoxicity was not inhibited by the addition of a 10,000-fold excess of octreotide acetate, implying that intracellular incorporation of small amounts of .sup.125 I-WOC-4a may be cytotoxic to SST-2-positive cells. This cryopreserved technique allows a long-term exposure to the radioligand but prevents cell proliferation that might mask the radioligand's cytotoxic effects.

DEPR:
For six months, pilot clinical trials were conducted in ten human patients with progressive metastatic indolent and symptomatic neuroendocrine cancers expressing the somatostatin receptor. Ten patients were given from one to six doses of .sup.111 In-pentetreotide. The first monthly dose was a bolus injection of 180 mCi. The second monthly dose was infusion of 180 mCi over 72 hr. The third monthly dose was infusion of 180 mCi over 24 hr. Thereafter, all monthly doses were infusion of 180 mCi over 24 hr. Clinical benefits (as evidenced by reduced pain, weight gain, reduced malaise, etc.) occurred in 6 of the 10 neuroendocrine (carcinoid/islet cell) patients. Partial radiographic responses (greater than 50% reduction in the product of perpendicular tumor diameters) occurred in 2 patients, and significant tumor necrosis developed in 7 of the 10 neuroendocrine patients. Treatment-related toxicity included 2 Grade III platelet, 1 Grade II WBC, 1 Grade I WBC and 2 Grade I Hb on the NCI (National Cancer Institute) grading scale. This experiment demonstrated that .sup.111 In pentetreotide at 180 mCi monthly doses was an effective and well-tolerated antineoplastic agent in some subjects with somatostatin receptor-expressing neoplasms.

DEPR:
Following a dosimetric .sup.111 In-pentetreotide scan and CT scans, subjects who demonstrate pathologic uptake of the radioisotope in areas corresponding to sites of metastatic disease will be eligible for the trial. After the bolus and infusional doses, responding subjects will be eligible to continue receiving monthly treatments until the disease progression or regression warrants stopping this therapy.

DEPR:
The first trial's major objective will be to determine the optimal rate of administration of 180 mCi doses of .sup.111 In-pentetreotide. Blood counts and blood chemistries will be analyzed prior to and weekly for 3 weeks after each treatment to identify any toxic effects. Nuclear scanning will occur daily for 3 days, and on days 7, 14, and 21 after the dose to determine uptake and excretion rates. Plasma samples will be collected and stored prior to therapy

and monthly for 6 months for assay of tumor-related biomarkers. Additional plasma and urine samples will be collected daily to calculate clearance rates of the radioligand. Chest, abdominal, and pelvic CT scans (to determine radiographic response rate) will be performed prior to the first and third doses. Radioactive uptake ratios (tumor to background), therapeutic ratios (tumor to kidney), excretion rates, and radioactive dose (areas under the mRoentgen/hr vs time curve) will be calculated.

DEPR:
The second trial's major objective will be to determine the maximal tolerated amount of .sup.111 In-pentetreotide that can be given. The following doses of .sup.111 In-pentetreotide will be evaluated in groups of 3 patients: 180, 360, 540, 720, 900, 1080, 1260 and 1440 mCi. The same blood counts, chemistries, nuclear scanning and radiographic assessments as described above will be performed. Should at least two drug-related NCI Grade IV toxicities occur, treatment will be terminated at that level. The number of courses that can be administered will then be determined as dose limiting.

DEPR:
Patients will be examined prior to each treatment and monthly for 3 months following therapy. Their quality of life will be assessed by clinical benefits, including reduced pain, weight gain, or reduced malaise. Clinical responses will be determined as either present, no change, or absent. Biochemical responses will be assessed by the measurement of plasma chromogranin A and/or 24 hr urinary 5-HIAA or other elevated disease-related markers. A partial response is defined as a 50% or greater decrease in a tumor marker. Radiographic responses will be determined by comparing the product of the perpendicular tumor diameters using the following WHO criteria: (a) Complete response: the complete disappearance of disease; (b) Partial response: a 50% or greater decrease; (c) Stable response: less than a 50% decrease and less than a 20% increase; and (d) Progressive disease: greater than a 20% increase.

DEPR:
The sample size for the phase I pilot study is determined by the objective of this study as stated above. In a preliminary trial, if the drug under investigation is 20% or more effective, one or more treatment successes should be seen in the first fourteen patients treated, with a confidence level of 95%. If a success is not seen in the first fourteen patients, the drug does not merit further investigational use. Thus, the sample size for this phase I study shall be fourteen evaluable patients. An additional 15 subjects will be studied after an interval analysis of the first 14 subjects. This latter group will assist in determining toxicity and efficacy. It is anticipated that indolent neuroendocrine neoplasms will dominate the first 15 slots since this population has shown the greatest potential of benefit.

DEPR:
These vein discs were placed into wells of three separate culture plates. One culture plate, the control sample, was allowed to grow without treatment. Another plate was treated with 50 .mu.Ci/mL of the radiolabeled somatostatin analog, .sup.111 In-pentetreotide; and the third plate treated with equivalent amounts of .sup.111 In-Cl. The discs were then incubated for fourteen days. After 14 days the culture plates were examined for the number of wells in which angiogenic growth was initiated. The percentage initiation is shown in FIG. 18. The % initiation seen in both treated culture plates was substantially less than the control plate. The lowest % initiation was seen in the culture plate treated with .sup.111 In-pentetreotide. The molar concentration of the radiolabeled somatostatin analog added to the culture plates was in the femtomolar range (10.sup.-15). This concentration is 1000.times. or more below the concentration of unlabeled somatostatin analog that is known to inhibit angiogenesis; a concentration of 10.sup.-5 M to 10.sup.-8 M. Thus any effect was due to the radiolabel and not just the presence of the somatostatin analog. Any difference between the .sup.111 In-Cl and .sup.111 In-pentetreotide is due to an effect of Auger emission on angiogenic cell growth through Auger effect on the DNA. Only the radiolabel

connected to the somatostatin analog would be incorporated into the DNA. Thus the greater decrease is due to this incorporation and the Auger emission on DNA.

DEPR:
Using a digital image analyzer, the mean area of the sprouting tissue surrounding the discs was measured. As shown in FIG. 19, the vessel area (mm.sup.2) was also substantially less in both treated culture plates. Again, the plate treated with the .sup.111 In-pentetreotide showed the least area of new growth.

DEPR:
To measure the growth rate of angiogenic vascular tissue, every two days during the 14-day incubation period, the length of sprouts were measured. The growth rate as measured by mm/day for all three culture plates is given in FIG. 20. Again, the growth rate in the two treated culture plates is substantially below that of the control. However, there is no difference in the growth rate between the two treated samples.

DEPR:
Other somatostatin analogs will be tested using the same human placental vascular discs. These discs will be placed into wells of two separate culture plates. One culture plate will be allowed to grow to maturity without treatment. The other culture plate will be exposed to various treatments: (1) radiolabeled somatostatin analog (.sup.125 I-WOC-4a, .sup.131 I-WOC-4a, .sup.111 In-DPTA-WOC-4a, .sup.111 In-DPTA-JIC-2D, .sup.125 I-JIC-2D, or dual labelled .sup.111 In-DPTA-.sup.125 I-WOC-4a or .sup.111 In-DPTA-.sup.125 I-JIC-2D,); (2) cold, unlabeled somatostatin analog (WOC-4a or JIC-2D); (3) radioisotope alone (.sup.125 I or .sup.131 I); (4) a combination of the radiolabeled somatostatin analog and its corresponding unlabeled analog (e.g., .sup.125 I-WOC-4a and WOC-4a); or (5) a combination of the cold, unlabeled somatostatin analog and the unbound radioisotope (e.g., .sup.125 I and WOC-4a). The discs will be incubated for three days with the analog present in a dose ranging from 10 to 1,000,000 counts per well. After three days fresh media will be added and the discs observed until maturity. The percentage of wells that initiate an angiogenic response will be calculated for non-treated and treated wells. The results from the different treatments will be analyzed with ANOVA.

DEPR:
Alternatively, to amplify the degree of cell destruction caused by the radioactivity, the vein discs will be cryoprotected and kept frozen in liquid nitrogen after a three day exposure to the radioligand. Freezing will inhibit cell division but will not affect radioactivity. Another set of plates will be constructed with identically treated vein discs but no radiation source. At the end of three days of treatment, these vein discs will be harvested, washed, and cryopreserved in tissue culture media containing 10% dimethylsulfoxide (DMSO). These vein discs will be cryopreserved in a controlled-rate freezer and stored in liquid nitrogen for 2 months, or for a period that is six times the physical half-life of the radioisotope used. At this time, the vein discs will be thawed and re-planted in fibrinogen gel-containing wells and allowed to grow as described above. After two weeks of growth, the treated and non-treated wells will be compared.

DETL:
TABLE 7 .sup.111 In-Pentetreotide Binding to Cellular DNA.sup.(1) IMR-32 CELLS SKNSH CELLS Protease Protease Treated Untreated Treated Untreated Experiment (CPM) (CPM) (CPM) (CPM) 1 10,276 11,512 122 316 2 9,564 10,122 412 319 3 12,648 14,566 208 220 Mean + S.D. 10,829 .+-. 1614 12,066 .+-. 2273 247 .+-. 149 285 .+-. 56 .sup.(1) Numbers represent the counts per minute (CPM) for 100 .mu.g samples of DNA for each cell type in three replicate experiments.

ORPL:
A. Kurtaran, et al., "Vasoactive Intestinal Peptide and Somatostatin Receptor Scintigraphy for Differential Diagnosis of Hepatic Carcinoid Metastasis," The

Journal of Nuclear Medicine, vol. 38, pp. 880-881 (1997).

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L11: Entry 21 of 37 File: USPT Mar 23, 1999

DOCUMENT-IDENTIFIER: US 5885547 A
TITLE: Particulate material

BSPR:
In one particular aspect, this invention relates to hollow or cup-shaped ceramic microspheres which consist of or comprise a radioactive material, and to the use of these radioactive microspheres in the treatment of cancer in humans and other mammals. In this aspect, the radioactive microspheres are designed to be administered into the arterial blood supply of the organ to be treated, whereby they become entrapped in the small blood vessels of the target organ and irradiate it. An alternate form of administration is to inject the radioactive microspheres directly into the tumour to be treated.

BSPR:
The particulate material of the present invention therefore has utility in the treatment of various forms of cancer and tumours, but particularly in the treatment of primary and secondary cancer of the liver and the brain. It is, however, to be understood that this invention is not limited to microspheres of radioactive material, and extends to microspheres of other ceramic materials which are suitable for use in the process described herein.

BSPR:
Many previous attempts have been made to locally administer radioactive materials to patients with cancer as a form of therapy. In some of these, the radioactive materials have been incorporated into small particles, seeds, wires and similar related configurations that can be directly implanted into the cancer. In other approaches, the radioactive materials have been formulated into microspheres of regular size for injection into the arterial blood supply of the target organ. When radioactive particles or microspheres are administered into the blood supply of the target organ, the technique has become known as Selective Internal Radiation Therapy (SIRT). Generally, the main form of application of SIRT has been its use to treat cancers in the liver.

BSPR:
There are many potential advantages of SIRT over conventional, external beam radiotherapy. Firstly, the radiation is delivered preferentially to the cancer within the target organ. Secondly, the radiation is slowly and continually delivered as the radionuclide decays. Thirdly, by manipulating the arterial blood supply with vasoactive substances (such as Angiotensin-2), it is possible to enhance the percentage of radioactive microspheres that go to the cancerous part of the organ, as opposed to the healthy normal tissues. This has the effect of preferentially increasing the radiation dose to the cancer while maintaining the radiation dose to the normal tissues at a lower level (Burton, M. A. et al.; Effect of Angiotensin-2 on blood flow in the transplanted sheep squamous cell carcinoma. Europ. J. Cancer Clin. Oncol. 1988, 24(8):1373-1376).

BSPR:
For radioactive microspheres to be used successfully for the treatment of cancer, the radiation emitted from the microspheres should be of high energy and short range. This ensures that the energy emitted from the microspheres will be deposited into the tissues immediately around the microspheres and not

into tissues which are not the target of the radiation treatment. There are many radionuclides that can be incorporated into microspheres that can be used for SIRT. Of particular suitability for use in this form of treatment are the unstable isotopes of yttrium (Y-90) and phosphorous (P-32), although other isotopes such as iodine can also be used. Yttrium-90 is the unstable isotope of yttrium-89 which can be manufactured by placing the stable yttrium-89 in a neutron beam. The yttrium-90 that is generated decays with a half life of 64 hours, while emitting a high energy pure beta radiation.

BSPR:
If the microspheres contain other radioactive substances that are not required for the radiation treatment of the target tissue, then unwanted and deleterious radiation effects may occur. It is therefore desirable to have microspheres of such a composition that they only contain the single desired radionuclide. In this treatment mode, it is desirable to have microspheres that emit high energy but short penetration beta-radiation which will confine the radiation effects to the immediate vicinity of the microspheres. For this purpose, yttrium-90 is the preferred radionuclide, although other radionuclides such as P-32 are also suitable.

BSPR:
Therefore, the ideal microspheres for use in this treatment mode will consist only of yttria, have a low density relative to pure yttria, be in the size range of from 20-80 micron, and be stable so that no material leaches from the microspheres when administered into the body of a human or other mammalian patient.

BSPR:
There have been several reports of clinical studies on the use of solid glass radioactive microspheres. In one report, ten patients with primary hepatocellular carcinoma were treated, however no patient had a complete or partial response (Shepherd, F. et al., Cancer, Nov. 1, 1992, Vol. 70, No. 9, pp 2250-2254).

BSPR:
A further development in order to overcome the problem of leaching, was the production of light polymeric ion-exchange microspheres that did not leach their yttrium content when injected into the body. Using these microspheres, a high objective response rate for patients with secondary cancer in the liver was obtained when the microspheres were injected into the hepatic artery (Gray, B. N. et al. Regression of liver metastases following treatment with Yttrium-90 microspheres. Aust. N.Z. J. Surg. 1992, 62:105-110). One disadvantage of such polymeric ion exchange microspheres is that the yttrium-90 radionuclide must be added to the microsphere after neutron activation of the stable isotope of yttrium-89. This requires the use of specialised facilities and potentially is hazardous to the manufacturing personnel. Furthermore, the polymeric microspheres contain only a low percentage of yttrium.

BSPR:
Using the technique described by Gray et al., other clinical studies in patients with secondary liver cancer have demonstrated a very high response rate using low density yttrium-90 containing microspheres. In one study in patients with metastatic liver cancer, the majority of patients benefited from treatment with radioactive microspheres with appropriate physical characteristics, specially when combined with perfusion of cytotoxic drugs into the arterial circulation of the liver (Gray, B. N. et al., supra).

BSPR:
In order to overcome the problem of leaching of radionuclide from ceramic microspheres, while at the same time maintaining the microspheres with a low density, the present invention provides microspheres with improved characteristics arising from the fact that the microspheres are either hollow or cup-shaped. These microspheres can be formulated to be of such a size, shape and density that they have improved distribution characteristics when

administered into the arterial supply of target organs to be treated. In addition, as they may be composed entirely of yttria, each microsphere can deliver a higher amount of ionising radiation than prior art microspheres. This, in turn, means that a lesser number can be administered to the target organ in order to deliver the same radiation dose. In another improvement, since the composition of the microspheres may be of pure yttria, unwanted ionising radiation emanating from unwanted radionuclides in the microspheres is thereby avoided. In another improvement, the microspheres can be neutron activated after manufacture, thereby improving the manufacture process.

BSPR:
In one embodiment of this invention, there is provided a method by which yttria can be thermally sprayed so as to form hollow or cup-shaped microspheres with the desired shape and density for use in the treatment of various forms of cancer and tumours, particularly in the liver and brain. These microspheres are composed of pure yttria, with a preferred size range of from 20 to 80 micron in diameter. The hollow or cup-shaped yttria microspheres are placed in a neutron beam to activate the yttria to the unstable isotope yttrium-90, and the radioactive microspheres can then be used in the treatment of cancers and/or tumours as described above.

DEPR:
The measurement of tumour response by objective parameters including reduction in tumour volume and serial estimations of serum carcino-embryonic antigen (CEA) levels, is an acceptable index of the ability of the treatment to alter the biological behaviour of the tumour.

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L11: Entry 5 of 37 File: USPT Jul 10, 2001

DOCUMENT-IDENTIFIER: US 6258338 B1
TITLE: Hollow or cup-shaped microparticles and methods of use

BSPR:
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BSPR:
There are many potential advantages of SIRT over conventional, external beam radiotherapy. Firstly, the radiation is delivered preferentially to the cancer within the target organ. Secondly, the radiation is slowly and continually delivered as the radionuclide decays. Thirdly, by manipulating the arterial blood supply with vasoactive substances (such as Angiotensin-2), it is possible to enhance the percentage of radioactive microspheres that go to the cancerous part of the organ, as opposed to the healthy normal tissues. This has the effect of preferentially increasing the radiation dose to the cancer while maintaining the radiation dose to the normal tissues at a lower level (Burton, M. A. et al.; Effect of Angiotensin-2 on blood flow in the transplanted sheep squamous cell carcinoma. Europ. J. Cancer Clin. Oncol. 1988, 24(8):1373-1376).

BSPR:
For radioactive microspheres to be used successfully for the treatment of cancer, the radiation emitted from the microspheres should be of high energy and short range. This ensures that the energy emitted from the microspheres will be deposited into the tissues immediately around the microspheres and not into tissues which are not the target of the radiation treatment. There are many radionuclides that can be incorporated into microspheres that can be used for SIRT. Of particular suitability for use in this form of treatment are the unstable isotopes of yttrium (Y-90) and phosphorous (P-32), although other isotopes such as iodine can also be used. Yttrium-90 is the unstable isotope

of yttrium-89 which can be manufactured by placing the stable yttrium-89 in a neutron beam. The yttrium-90 that is generated decays with a half life of 64 hours, while emitting a high energy pure beta radiation.

BSPR:
If the microspheres contain other radioactive substances that are not required for the radiation treatment of the target tissue, then unwanted and deleterious radiation effects may occur. It is therefore desirable to have microspheres of such a composition that they only contain the single desired radionuclide. In this treatment mode, it is desirable to have microspheres that emit high energy but short penetration beta-radiation which will confine the radiation effects to the immediate vicinity of the microspheres. For this purpose, yttrium-90 is the preferred radionuclide, although other radionuclides such as P-32 are also suitable.

BSPR:
Therefore, the ideal microspheres for use in this treatment mode will consist only of yttria, have a low density relative to pure yttria, be in the size range of from 20.gtoreq.80 micron, and be stable so that no material leaches from the microspheres when administered into the body of a human or other mammalian patient.

BSPR:
There have been several reports of clinical studies on the use of solid glass radioactive microspheres. In one report, ten patients with primary hepatocellular carcinoma were treated, however no patient had a complete or partial response (Shepherd, F. et al., Cancer, Nov. 1, 1992, Vol. 70, No. 9, pp 2250-2254).

BSPR:
A further development in order to overcome the problem of leaching, was the production of light polymeric ion-exchange microspheres that did not leach their yttrium content when injected into the body. Using these microspheres, a high objective response rate for patients with secondary cancer in the liver was obtained when the microspheres were injected into the hepatic artery (Gray, B. N. et al.. Regression of liver metastases following treatment with Yttrium-90 microspheres. Aust. N. Z. J. Surg. 1992, 62:105-110). One disadvantage of such polymeric ion exchange microspheres is that the yttrium-90 radionuclide must be added to the microsphere after neutron activation of the stable isotope of yttrium-89. This requires the use of specialised facilities and potentially is hazardous to the manufacturing personnel. Furthermore, the polymeric microspheres contain only a low percentage of yttrium.

BSPR:
Using the technique described by Gray et al., other clinical studies in patients with secondary liver cancer have demonstrated a very high response rate using low density yttrium-90 containing microspheres. In one study in patients with metastatic liver cancer, the majority of patients benefited from treatment with radioactive microspheres with appropriate physical characteristics, especially when combined with perfursion of cytotoxic drugs into the arterial circulation of the liver (Gray, B. N. et al., supra).

BSPR:
In order to overcome the problem of leaching of radionuclide from ceramic microspheres, while at the same time maintaining the microspheres with a low density, the present invention provides microspheres with improved characteristics arising from the fact that the microspheres are either hollow or cup-shaped. These microspheres can be formulated to be of such a size, shape and density that they have improved distribution characteristics when administered into the arterial supply of target organs to be treated. In addition, as they may be composed entirely of yttria, each microsphere can deliver a higher amount of ionising radiation than prior art microspheres. This, in turn, means that a lesser number can be administered to the target organ in order to deliver the same radiation dose. In another improvement,

since the composition of the microspheres may be of pure yttria, unwanted ionising radiation emanating from unwanted radionuclides in the microspheres is thereby avoided. In another improvement, the microspheres can be neutron activated after manufacture, thereby improving the manufacture process.

BSPR:
In one embodiment of this invention, there is provided a method by which yttria can be thermally sprayed so as to form hollow or cup-shaped microspheres with the desired shape and density for use in the treatment of various forms of cancer and tumours, particularly in the liver and brain. These microspheres are composed of pure yttria, with a preferred size range of from 20 to 80 micron in diameter. The hollow or cup-shaped yttria microspheres are placed in a neutron beam to activate the yttria to the unstable isotope yttrium-90, and the radioactive microspheres can then be used in the treatment of cancers and/or tumours as described above.

DEPR:
The measurement of tumour response by objective parameters including reduction in tumour volume and serial estimations of serum carcino-embryonic antigen (CEA) levels, is an acceptable index of the ability of the treatment to alter the biological behaviour of the tumour.

CLPR:
3. A method according to claim 1, wherein the radiation therapy comprises treatment of cancer or tumours in the patient.

CLPR:
4. A method according to claim 3, wherein the radiation therapy comprises treatment of primary or secondary cancer of the liver of the patient.

WEST

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USPT,PGPB,JPAB,EPAB,DWPI,TDBD	treat$6 or prevent$5	5193940	L10
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	l8 and l6	37	L9
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	metastasis	11738	L8
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	s metastatis	0	L7
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	l5 same l2	187	L6
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	angiotensin	9703	L5
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	l1 and l2	46	L4
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	l1 same l2	1	L3
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	cancer	88303	L2
USPT,PGPB,JPAB,EPAB,DWPI,TDBD	angiotension	415	L1

WEST

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L11: Entry 35 of 37 File: DWPI Oct 13, 1998

DERWENT-ACC-NO: 1998-446767
DERWENT-WEEK: 199851

TITLE: Sustained release microsphere formulation of peptide - prepared from emulsion of peptide and pamoic acid in biodegradable polymer, used for luteinising hormone release hormone (ant)agonists

INVENTOR: IGARI, Y; KAMEI, S ; OHTA, T ; SAIKAWA, A

PATENT-ASSIGNEE:

ASSIGNEE	CODE
TAKEDA CHEM IND LTD	TAKE

PRIORITY-DATA: 1997JP-0015203 (January 29, 1997)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
JP 10273447 A	October 13, 1998		019	A61K038/00
WO 9832423 A1	July 30, 1998	E	064	A61K009/16
AU 9856783 A	August 18, 1998		000	A61K009/16

DESIGNATED-STATES: AL AM AU AZ BA BB BG BR BY CA CN CU CZ EE GE GW HU ID IL IS KG KR KZ LC LK LR LT LV MD MG MK MN MX NO NZ PL RO RU SG SI SK SL TJ TM TR TT UA US UZ VN YU AT BE CH DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
JP10273447A	January 28, 1998	1998JP-0014698	
WO 9832423A1	January 28, 1998	1998WO-JP00339	
AU 9856783A	January 28, 1998	1998AU-0056783	
AU 9856783A		WO 9832423	Based on

INT-CL (IPC): A61K 9/16; A61K 9/50; A61K 9/52; A61K 38/00; A61K 38/11; A61K 38/22; A61K 38/23; A61K 38/24; A61K 38/27; A61K 38/28; A61K 38/35; A61K 47/12; A61K 47/46

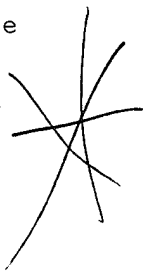
ABSTRACTED-PUB-NO: WO 9832423A
BASIC-ABSTRACT:

Production of sustained release microspheres comprises emulsification of a physiologically active peptide (or its salt) and a pamoic acid (or its alkali metal salt) with a biodegradable polymer. The peptide salt is not pamoate.

Also claimed are the microspheres obtained.

USE - The method is used to produce microspheres containing LH-RH agonists and antagonists (especially 5-oxo-Pro-His-Trp-Ser-Tyr-DLeu-Leu-Ar g-Prop-NHEt (Ia)

or its salt, notably the acetate (Ib)), for the treatment and prevention of prostate cancer and hypertrophy, endometritis, hysteromyoma, dysmenorrhoea, precocious puberty or breast cancer, or as a contraceptive agent (claimed).



The peptides are preferably hormones with basic groups which can form insoluble salts with the pamoic acid to provide the control, useful in clinical and veterinary medicine, including for metrofibroma, cancers of gall bladder, cervix, colon/rectum, and ovary, small and non-small lung cancer, lymphatic or myelocytic leukaemia, malignant melanoma, Hodgkin's disease, metastasis, gastritis, multiple myeloma, non-Hodgkin lymphoma, ulcers, systemic fungal infections, valvular heart disease, mastopathy, polycystic ovary, infertility, anovulation, induced ovulation, acne, amenorrhoea, hyperandrogenaemia, hypertrichosis, AIDS from T-cell production mediated by thymic blastogenesis, treatment of male sex criminals, and premenstrual syndrome, and in vitro fertilisati on. Other peptide hormones include insulin, somatostatin, growth hormones (GH) and GH-RH, ACTH, prolactin, TRH, TSH, FSH, MSH, erythropoiet in, vasopressin, oxytocin, calcitonin, glucagon, gastrin, angiotensin, enkephalin, endorphin, interferon, interleukin, TNF, CSF, ANF, bradykinin, cholecystokinin, and nerve growth and nutrition factors.

ADVANTAGE - The microspheres give controlled release of active peptide over a period of weeks or months in vivo. Quite high concentrations of active peptide, up to nearly 50%, can be formulated in the polymer.

CHOSEN-DRAWING: Dwg.0/0

TITLE-TERMS: SUSTAINED RELEASE MICROSPHERE FORMULATION PEPTIDE PREPARATION EMULSION PEPTIDE PAMOIC ACID BIODEGRADABLE POLYMER LUTEINISING HORMONE RELEASE HORMONE ANT AGONIST

DERWENT-CLASS: A96 B04 B07

CPI-CODES: A09-A07; A12-V01; B04-C01; B04-C03; B12-M10A;

CHEMICAL-CODES:

Chemical Indexing M1 *01*
Fragmentation Code
D011 D601 F012 F014 F423 F521 G013 G100 H1 H100
H181 H4 H401 H441 H481 H8 J0 J011 J1 J111
J171 J3 J311 J390 J5 J521 K0 L2 L250 L941
M210 M212 M273 M280 M281 M312 M314 M315 M320 M321
M332 M333 M340 M342 M343 M349 M371 M381 M391 M423
M431 M510 M511 M520 M521 M530 M531 M540 M620 M630
M640 M650 M782 M903 M904 P633 P843 R052 V925
Markush Compounds
199838-FDF01-M

Chemical Indexing M1 *02*
Fragmentation Code
H4 H401 H481 H8 J0 J011 J1 J171 M280 M311
M321 M342 M349 M381 M391 M416 M423 M431 M620 M782
M903 M904 M910 P633 P843 R052 V743
Specfic Compounds
00448M 00448Q
Registry Numbers
0448S 0448U

Chemical Indexing M1 *03*
Fragmentation Code
H4 H401 H481 H8 J0 J011 J1 J171 M280 M312
M321 M331 M340 M342 M349 M381 M391 M416 M423 M431
M620 M782 M903 M904 M910 P633 P843 R052 V743
Specfic Compounds
00009M 00009Q

Registry Numbers
0009S 0009U

Chemical Indexing M6 *04*
Fragmentation Code
M903 P633 P843 R052 R112 R280

UNLINKED-DERWENT-REGISTRY-NUMBERS: 0009S; 0009U ; 0448S ; 0448U

ENHANCED-POLYMER-INDEXING:
Polymer Index [1.1] 018 ; G2108*R D01 D60 F35 ; P1978*R P0839 D01 D50 D63 F41 ; H0000 ; H0011*R ; S9999 S1605*R ; S9999 S1627 S1605 ; S9999 S1423 S1401 Polymer Index [1.2] 018 ; R00448 G2108 D01 D11 D10 D50 D60 D82 F27 F26 F36 F35 ; R00009 G2108 D01 D11 D10 D50 D60 D83 F27 F26 F36 F35 ; P1978*R P0839 D01 D50 D63 F41 ; H0022 H0011 ; S9999 S1605*R ; S9999 S1627 S1605 ; S9999 S1423 S1401 Polymer Index [1.3] 018 ; R00009 G2108 D01 D11 D10 D50 D60 D83 F27 F26 F36 F35 ; P1978*R P0839 D01 D50 D63 F41 ; H0000 ; S9999 S1605*R ; S9999 S1627 S1605 ; S9999 S1423 S1401 Polymer Index [1.4] 018 ; ND01 ; ND07 ; Q9999 Q7250 ; Q9999 Q8037 Q7987 ; N9999 N7330 N7023 ; N9999 N5890 N5889 ; N9999 N6860 N6655 ; N9999 N6780*R N6655 ; B9999 B3021 B3010 ; B9999 B5094 B4977 B4740 ; B9999 B5209 B5185 B4740 ; K9665 Polymer Index [1.5] 018 ; D01 ; R00345 G1978 D01 D11 D10 D50 D69 D81 Cl 7A ; A999 A475 Polymer Index [1.6] 018 ; A999 A635 A624 A566 ; S9999 S1616 S1605 Polymer Index [2.1] 018 ; P1707 P1694 D01 ; S9999 S1616 S1605 ; A999 A635 A624 A566 ; A999 A782

SECONDARY-ACC-NO:
CPI Secondary Accession Numbers: C1998-135447

L11: Entry 15 of 37 File: USPT Feb 15, 2000

DOCUMENT-IDENTIFIER: US 6025337 A
TITLE: Solid microparticles for gene delivery

BSPR:
Controlled drug delivery has significantly improved the success of many drug therapies (Langer, R., 1990, New methods of drug delivery, Science, 249:1527-33; Poznansky, et al., 1984, Biological approaches to the controlled delivery of drugs: a critical review, Pharmacol. Rev., 36:277-336). A major goal of drug delivery is to localize the drug to the target site. These targeted delivery systems often take the form of injectables composed of liposomes (Gregoriadis, G., 1988, Liposomes as Drug Carriers, New York: Wiley; Litzinger, et al., 1992, Phosphatidylethanolamine liposomes: drug delivery, gene transfer and immunodiagnostic applications, Biochimica et Biophysica Acta., 1113:201-27) and microspheres made of proteins (Cummings, et al., 1991, Covalent coupling of doxorubicin in protein microspheres is a major determinant of tumor drug deposition, Biochem. Pharm., 41:1849-54; Verrijik, et al., 1991, Polymer-coated albumin microspheres as carriers for intravascular tumor targeting of cisplatin, Cancer Chemother. and Pharm., 29:117-21; Tabata, et al., 1988, Potentiation of antitumor activity of macrophages by recombinant interferon alpha A/D contained in gelatin microspheres, Jpn. J. Cancer Res., 79:636-646), polysaccharides (Rongved, et al., 1991, Crossed-linked, degradable starch microspheres as carriers of paramagnetic resonance imaging: synthesis, degradation, and relaxation properties, Carbohydrate Res., 145:83-92; Carter, et al., 1991, The combination of degradable starch microspheres and angiotensin II in the manipulation of drug delivery in an animal model of colorectal metastasis, British J. Cancer, 65:37-9), and synthetic polymers (Davis, et al., 1984, Microspheres and Drug Therapy, Amsterdam; Eldridge, et al., 1991, Biodegradable microspheres as a vaccine delivery system, Molec. Immunology, 28:287-94; Pappo, et al., 1991, Monoclonal antibody-directed targeting of fluorescent polystyrene microspheres to Peyer's patch M cells, Immunology, 73:277-80). Polymeric systems share some of the advantages of liposomal systems such as altered pharmacokinetics and biodistribution. While liposomes might have better prospects of biocompatibility and potential for fusion with cells, polymeric microspheres have more controllable release kinetics, better stability in storage, and higher drug-loading levels for some classes of compounds.

DEPR:
An attractive microparticle delivery system requires a delicate balance among factors such as the simplicity of preparation, cost effectiveness, nucleic acids loading level, controlled release ability, storage stability, and immunogenicity of the components. The gene delivery system described here may offer advantages compared to other particulate delivery systems, including the liposomal system. The problems of instability, low loading level, and controlled release ability are better resolved with the polymeric microparticle systems. Gelatin has received increasing biologic use ranging from surgical tissue adhesive (Weinschelbaum, et al., 1992, Surgical treatment of acute type A dissecting aneurysm with preservation of the native aortic valve and use of biologic glue. Follow-up to 6 years, J. Thorac. Cardiovasc. Surg., 130:369-74) to quantitative immunohistochemical assays (Izumi, et al., 1990, Novel gelatin particle agglutination test for serodiagnosis of leprosy in the field, J. Clinical Microbiol., 28:525-9) and as drug delivery vehicle

(Tabata, et al., 1991, Effects of recombinant alpha-interferon-gelatin conjugate on in vivo murine tumor cell growth, Cancer Res., 51:5532-8), due to its biocompatibility and enzymatic degradability in vivo. Compared to other synthetic polymeric systems, such as the extensively studied polylactic/polyglycolic copolymers, the mild conditions of microparticle formulation are appealing. Unlike the solvent evaporation and hot-melt techniques used to formulate synthetic polymeric microparticles, complex coacervation requires neither contact with organic solvents nor heat. It is also particularly suitable for encapsulating bio-macromolecules such as nucleic acids not only through passive solvent capturing but also by direct charge-charge interactions.

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NEWS  3  Feb 06      Engineering Information Encompass files have new names
NEWS  4  Feb 16      TOXLINE no longer being updated
NEWS  5  Apr 23      Search Derwent WPINDEX by chemical structure
NEWS  6  Apr 23      PRE-1967 REFERENCES NOW SEARCHABLE IN CAPLUS AND CA
NEWS  7  May 07      DGENE Reload
NEWS  8  Jun 20      Published patent applications (A1) are now in USPATFULL
NEWS  9  JUL 13      New SDI alert frequency now available in Derwent's
                     DWPI and DPCI
NEWS 10  Aug 23      In-process records and more frequent updates now in
                     MEDLINE
NEWS 11  Aug 23      PAGE IMAGES FOR 1947-1966 RECORDS IN CAPLUS AND CA
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NEWS 13  Sep 17      IMSworld Pharmaceutical Company Directory name change
                     to PHARMASEARCH
NEWS 14  Oct 09      Korean abstracts now included in Derwent World Patents
                     Index
NEWS 15  Oct 09      Number of Derwent World Patents Index updates increased
NEWS 16  Oct 15      Calculated properties now in the REGISTRY/ZREGISTRY File
NEWS 17  Oct 22      Over 1 million reactions added to CASREACT
NEWS 18  Oct 22      DGENE GETSIM has been improved

NEWS EXPRESS  August 15 CURRENT WINDOWS VERSION IS V6.0c,
              CURRENT MACINTOSH VERSION IS V6.0 (ENG) AND V6.0J (JP),
              AND CURRENT DISCOVER FILE IS DATED 07 AUGUST 2001
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L1 1166 ANGIOTENSION?

=> s angiotensin?
L2 167679 ANGIOTENSIN?

=> s cancer?
L3 909955 CANCER?

=> s l2 (p) l3
L4 511 L2 (P) L3

=> s metastasis?
L5 182752 METASTASIS?

=> s l5 and l4
L6 37 L5 AND L4

=> s treat? pr prevent?
L7 0 TREAT? PR PREVENT?

=> s treat? or prevent?
L8 6693676 TREAT? OR PREVENT?

=> s l8 and l6
L9 22 L8 AND L6

=> dup rem l9
PROCESSING COMPLETED FOR L9
L10 20 DUP REM L9 (2 DUPLICATES REMOVED)

=> d 1-20 ab,bib

L10 ANSWER 1 OF 20 MEDLINE
AB Nontypical chemotherapy regimens exist for advanced pancreatic **cancer**. We herein report a 62-year-old man whose nonresectable pancreatic **cancer** was **treated** effectively with a new method of intra-arterial regional chemotherapy with **angiotensin** -II (AT-II). The patient was admitted to our hospital with obstructive jaundice and anorexia. He was diagnosed as having inoperable advanced pancreatic **cancer** with liver **metastasis**. Enteric-coated tegafur/uracil (400 mg) was administered for 3 weeks. Simultaneously, intraarterial infusion with 5-fluorouracil (500 mg) and infusion of methotrexate (100 mg) with 50 micrograms of AT-II was given every week. A catheter connected to a subcutaneously implanted port system was placed into the common hepatic artery. As a result of this

treatment, the maximum diameter of the pancreatic tumor decreased from 3 cm to 2 cm on the CT-scan. Serum carbohydrate antigen 19-9 (CA19-9) decreased from 24,000 U/ml to 186 U/ml. Moreover, the performance status of patient also improved, and he was discharged from our hospital despite his terminal **cancer**. This regimen could well be effective in cases of advanced pancreatic **cancer**.

AN 2001249367 MEDLINE
DN 21228541 PubMed ID: 11329788
TI A case of successful management of nonresectable pancreas **cancer** with liver **metastasis** by intra-arterial infusion chemotherapy with **angiotensin**-II and administration of tegafur/uracil.
AU Ishikawa T; Sato S; Matsuzawa J; Mita Y; Matsui S; Tashiro K; Tashiro S; Matsuki H
CS Dept. of Internal Medicine, Tashiro Hospital for Gastroenterology.
SO GAN TO KAGAKU RYOHO [JAPANESE JOURNAL OF CANCER AND CHEMOTHERAPY], (2001 Apr) 28 (4) 521-5.
Journal code: 6T8; 7810034. ISSN: 0385-0684.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
LA Japanese
FS Priority Journals
EM 200105
ED Entered STN: 20010517
Last Updated on STN: 20010517
Entered Medline: 20010510

L10 ANSWER 2 OF 20 CA COPYRIGHT 2001 ACS
AB A method of **treatment** or **prevention** of **metastasis** of **cancer** cells comprises administration of an effective amt. of an **angiotensin** to a patient. The use of an **angiotensin** in the prepn. of a medicament for the **prevention** of **metastasis** of **cancer** cells is also described. A second aspect of the invention is a method of inducing expression of .beta.1-integrin mols. in **cancer** cells to **prevent** or **treat metastasis** by administering an effective amt. of an **angiotensin**.

AN 132:161695 CA
TI **Cancer treatment** with an **angiotensin**
IN Vinson, Gavin Paul; Puddefoot, John Richard; Berry, Miles Gordon
PA Queen Mary & Westfield College, UK
SO PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000010590	A2	20000302	WO 1999-GB2727	19990818
	WO 2000010590	A3	20000518		
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 9954348	A1	20000314	AU 1999-54348	19990818

EP 1104305 A2 20010606 EP 1999-940353 19990818
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO
PRAI GB 1998-18023 A 19980818
GB 1998-20000 A 19980914
WO 1999-GB2727 W 19990818

L10 ANSWER 3 OF 20 MEDLINE
AB A 62-year-old woman suffering from gallbladder stone had a remarkably high preoperative CEA level of 525 ng/ml. Computed tomography revealed swollen mediastinal lymph nodes. Lymph node biopsy during thoracotomy led to a diagnosis of **metastasis** from poorly differentiated adenocarcinoma. Although thorough examinations were performed, the origin of the adenocarcinoma could not be detected. In this case, induced hypertensive chemotherapy with **angiotensin** II was effective. The mediastinal lymph nodes diminished remarkably and the patient's CEA level decreased to 22 ng/ml. Induced hypertensive chemotherapy with **angiotensin** II might be a useful **treatment** for **cancer** metastases of unknown origin.
AN 2001080190 MEDLINE
DN 21022963 PubMed ID: 11142174
TI Induced hypertensive chemotherapy with angiotensin II found effective for mediastinal lymph node metastases of unknown origin.
AU Ida K; Kamiya T
CS Dept. of Surgery, Kosai General Hospital.
SO GAN TO KAGAKU RYOHO [JAPANESE JOURNAL OF CANCER AND CHEMOTHERAPY], (2000 Dec) 27 (14) 2263-6.
Journal code: 6T8. ISSN: 0385-0684.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
LA Japanese
FS Priority Journals
EM 200101
ED Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010111

L10 ANSWER 4 OF 20 MEDLINE
AB AIMS: Integrins are a major family of cell adhesion molecules whose function is perturbed in tumour invasion and **metastasis**. **Angiotensin** II (A II) is well-known in the systemic control of water and electrolyte homeostasis and haemodynamics, but recent evidence points to an additional local renin-**angiotensin** system (RAS) with possible long-term trophic effects including carcinogenesis.
METHODS: The effect of **angiotensin** II on MCF-7 human breast **cancer** cell line integrin expression was evaluated with immunocytochemistry (ICC) and immunoprecipitation (IP). RESULTS: The experiments demonstrated a 1.40 +/- 0.14-fold increase in beta, integrin expression on MCF-7 cells following **treatment** with A II. CONCLUSIONS: These findings report the first evidence of an association between integrins and the RAS in human breast **cancer** cells and suggest a novel research avenue for future anti-metastatic strategies, through the manipulation of cell adhesion mechanics, in the management of invasive human breast **cancer**.
AN 2000181103 MEDLINE
DN 20181103 PubMed ID: 10718175
TI Integrin beta1 upregulation in MCF-7 breast **cancer** cells by **angiotensin** II.

AU Berry M G; Goode A W; Puddefoot J R; Vinson G P; Carpenter R
CS Department of Surgery, St Bartholomew's and the Royal London School of Medicine and Dentistry, St Bartholomew's Hospital, UK.
SO EUROPEAN JOURNAL OF SURGICAL ONCOLOGY, (2000 Feb) 26 (1) 25-9.
Journal code: EUR; 8504356. ISSN: 0748-7983.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200003
ED Entered STN: 20000330
Last Updated on STN: 20000330
Entered Medline: 20000321

L10 ANSWER 5 OF 20 CA COPYRIGHT 2001 ACS
AB Title compds. R2C(O)NHCH(R1)CH2N(C(O)R3)CH(R)CO2H [(I); R,R1 independently = (substituted)(branched) alkyl, alkylaryl, alkyl-hetaryl, (substituted) aryl or hetaryl; R2 = fluorenyl-methoxy, 2-fluorenyl-Et, R4CH2CH(SY), naphthyl, quinolinyl; R3 = (substituted) aryl or O, S, or N-hetaryl; R4 = alkyl, alkylaryl, aryl, hetaryl; Y = H, CH3C(O)], useful as endothelin inhibitors in the **treatment** of diseases such as hypertension, myocardial infarction, chronic heart insufficiency, angina pectoris, acute or chronic kidney disease, cerebral vasospasm or ischemia, subarachnoidal hemorrhage, migraine, asthma, atherosclerosis, endo-toxemic shock or organ failure, intravascular coagulation, prostatic hyperplasty or **cancer**, **metastasis** and growth of mesenchymal tumors, pancreatitis, and gastrointestinal ulcers, were synthesized and tested. Thus, resin-supported L-phenylalanine and N-Fmoc-L-phenylalaninal were reacted and the product condensed with 5-chloro-2-thiophen-carbonyl chloride, then freed from the resin support to give I [R, R1 = (S)-CH2Ph; R2 = fluorenyl-methoxy; R3 = (5-chloro)thiophen-2-yl; (II)]. In in vitro tests, II had IC50 2.mu.m against ECE, while its IC50 against other proteases (**angiotensin** converting enzyme, neutral endopeptidase) was >100 .mu.m.
AN 130:267770 CA
TI Synthesis of N,N-disubstituted amino acids as endothelin inhibitors with pharmaceutical effects
IN Puhl, Michael; Zechel, Johann-Christian; Ditrich, Klaus; Hillen, Heinz; Kohl, Tanja; Erhardt, Melanie; Hergenroeder, Stefan; Markert, Claus Otto
PA BASF A.-G., Germany
SO Ger. Offen., 12 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 19745146	A1	19990415	DE 1997-19745146	19971014
	WO 9919320	A1	19990422	WO 1998-EP5945	19980918
	W: AL, AU, BG, BR, BY, CA, CN, CZ, GE, HU, ID, IL, JP, KR, KZ, LT, LV, MK, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, US, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	AU 9910235	A1	19990503	AU 1999-10235	19980918
	EP 1023282	A1	20000802	EP 1998-952597	19980918
	R: AT, BE, CH, DE, ES, FR, GB, IT, LI, NL, SE, FI				

	BR 9813037	A	20000815	BR 1998-13037	19980918
	JP 2001519427	T2	20011023	JP 2000-515892	19980918
	NO 2000001846	A	20000410	NO 2000-1846	20000410
PRAI	DE 1997-19745146	A	19971014		
	WO 1998-EP5945	W	19980918		

OS MARPAT 130:267770

L10 ANSWER 6 OF 20 MEDLINE

AB The theoretical purpose of induced hypertensive chemotherapy used together with injection of **Angiotensin** II is to increase the delivery of anticancer drug to the target tumor tissue by increasing blood flow in the tumor. **Angiotensin** II (50 micrograms) was dissolved in 50 ml of normal saline, and given through a peripheral vein by a microinfusion pump. When systolic pressure rose to about 140 to 150 mmHg, mitomycin C (10 to 20 mg/body) was given for 10 minutes via implanted port, whose tip was located in hepatic artery, followed by continuous infusion of 5-FU at 250 mg/day for 5 days. Response could be measured in 7 of all 10 cases (70.0%), CR was found in 4 and PR in 3. As for complications, one case of pseudo-aneurysm and one case of bile duct necrosis owing to drug toxicity were observed. Bone metastases or carcinomatous peritonitis occurred after a few months in two CR cases. We concluded that this mode of chemotherapy was a useful measure for the **treatment** of liver metastases from gastric **cancer**.

AN 1998369464 MEDLINE

DN 98369464 PubMed ID: 9703841

TI Intrahepatic arterial infusion chemotherapy with **angiotensin** II for liver **metastasis** from gastric **cancer**.

AU Iwasaki Y; Kitamura M; Arai K

CS Dept. of Surgery, Tokyo Metropolitan Komagome Hospital.

SO GAN TO KAGAKU RYOHO [JAPANESE JOURNAL OF CANCER AND CHEMOTHERAPY], (1998 Jul) 25 (9) 1412-5.
Journal code: 6T8; 7810034. ISSN: 0385-0684.

CY Japan

DT Journal; Article; (JOURNAL ARTICLE)

LA Japanese

FS Priority Journals

EM 199808

ED Entered STN: 19980903
Last Updated on STN: 20000303
Entered Medline: 19980821

L10 ANSWER 7 OF 20 MEDLINE

AB This is a report of a 62-year-old woman whose non-resectable pancreatic **cancer** had been **treated** effectively by a new method of intra-arterial regional chemotherapy for more than 4 years. A catheter was placed into the celiac artery during laparotomy, and an intra -arterial chemotherapy (methotrexate (50 mg) and **Angiotensin**-II (AT-II, 5 micrograms)) has been repeated every other week (108 times) in addition to the external beam therapy (50 Gy). Both pain relief and "partial response" in the size of tumor have been obtained, with no hepatic **metastasis** or adverse effect. She died of brain **metastasis** at 51 postoperative months. Autopsy revealed that the pancreatic tumor was mostly replaced by fibrous connective tissues. Scintigraphic study

indicated that the intra-arterial infusion of AT-II increased the blood flow in the tumor but decreased it in the surrounding non-**cancerous** tissues. This seemed to explain the effective loco-regional control in the present case.

AN 97007630 MEDLINE
DN 97007630 PubMed ID: 8854821
TI A case of non-resectable pancreatic **cancer** surviving more than 4 years by intra-arterial infusion chemotherapy with **angiotensin** -II.
AU Tsuji Y; Ohigashi H; Ishikawa O; Yasuda T; Nakano H; Nakamori S; Kameyama M; Hiratsuka M; Sasaki Y; Kabuto T; Furukawa H; Imaoka S; Iwanaga T
CS Dept. of Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases.
SO GAN TO KAGAKU RYOHO [JAPANESE JOURNAL OF CANCER AND CHEMOTHERAPY], (1996 Sep) 23 (11) 1617-20.
Journal code: 6T8; 7810034. ISSN: 0385-0684.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
LA Japanese
FS Priority Journals
EM 199611
ED Entered STN: 19961219
Last Updated on STN: 19961219
Entered Medline: 19961120

L10 ANSWER 8 OF 20 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 1
AB Background/Aims: In order to deliver the anticancer drugs more selectively into the **cancer** tissues, we have developed a new method of intra-arterial regional chemotherapy for locally unresectable **cancer** of the exocrine pancreas. Materials and Methods: This method involved placing the catheters selectively into the splenic artery and/or into the gastroduodenal artery during laparotomy. Postoperatively, via the catheter, we infused 50100 mg of Methotrexate mixed with 10 mu-g of **Angiotensin**-II with an intent of increasing the blood flow in the tumor tissue but decreasing that to the non-tumor tissues. Simultaneously, a bolus iv-infusion of 5-fluorouracil (5-Fu, 500 mg) was performed. One day after each chemotherapy, citrovorum factor (Leucovorin, 30mg) was given per orally. For 15 patients with locally non-resectable pancreatic **cancer**, this **treatment** was repeated weekly or biweekly at our out-patient clinic. Results: As a result, the toxicity was so slight that all patients could tolerate this **treatment** as long as the catheter was patent (11 +- 8 postoperative months). The survival period was 16+-9 months (range: 5-36 months; median: 14 months), and one-, two- and three year survival rates were 60%, 23% and 11%, respectively. Patients could take care of themselves within 12+-9 months, and either complete (50%) or partial (50%) pain-relief was obtained among the 12 patients with severe pain. Only one patient experienced local tumor regression during the chemotherapy, and the incidence of liver **metastasis** was as low as 13%. Conclusions: Comparing with the previously reported data in the traditional chemo- and/or radio-therapies, we consider that our method of intra-arterial chemotherapy is quite useful not only for the prolongation of patient's survival but also for improving the quality of life. Thus, this new **treatment** seems worthy of entering into the prospective randomized study.
AN 1996:313674 BIOSIS
DN PREV199699036030
TI A new method of intra-arterial regional chemotherapy with more selective

drug delivery for locally advanced pancreatic cancer.
AU Ohigashi, Hiroaki (1); Ishikawa, Osamu; Imaoka, Shingi; Sasaki, Yo; Kabuto, Toshiyuki; Kameyama, Masao; Furukawa, Hiroshi; Hiratuka, Masahiro; Nakamori, Syoji; Nakano, Hirohumi; Yasuda, Takusi; Iwanaga, Takeshi
CS (1) Dep. Surg., Osaka Medical Center Cancer Cardiovasc. Dis., 1-3-3 Nakamichi, Higashinari-ku, Osaka 537 Japan
SO Hepato-Gastroenterology, (1996) Vol. 43, No. 8, pp. 338-345. ISSN: 0172-6390.
DT Article
LA English

L10 ANSWER 9 OF 20 MEDLINE
AB A 71-year-old woman underwent subtotal distal gastrectomy for II a+ II c type early **cancer** of the gastric antrum. Histological type was poorly differentiated adenocarcinoma with medullary proliferation, and the lesion invaded the submucosal layer. Two years and 6 months after the operation, multiple liver tumors were found on the CT scan. A surgical resection of the liver tumor was performed. Microscopically, the liver tumors were compatible with gastric **cancer**. The remnant liver metastases were **treated** by intrahepatic infusion chemotherapy with **Angiotensin** II human (Delivert) using a subcutaneous implanted pump. The liver metastases disappeared on the CT scan after 3 courses of chemotherapy, but bone **metastasis** occurred after 2 months. This mode of chemotherapy was therefore considered a useful **treatment** for liver **metastasis** in gastric **cancer** . We concluded that not only intrahepatic infusion chemotherapy with **Angiotensin** II human but also another systemic chemotherapy was necessary to **treat** patients with liver **metastasis** in gastric **cancer**.
AN 96006484 MEDLINE
DN 96006484 PubMed ID: 7574790
TI A case of intrahepatic infusion chemotherapy with **angiotensin** II human for liver **metastasis** from early gastric **cancer**.
AU Iwasaki Y; Kitamura M; Arai K
CS Dept. of Surgery, Tokyo Metropolitan Komagome Hospital.
SO GAN TO KAGAKU RYOHO [JAPANESE JOURNAL OF CANCER AND CHEMOTHERAPY], (1995 Sep) 22 (11) 1674-8. Journal code: 6T8; 7810034. ISSN: 0385-0684.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
LA Japanese
FS Priority Journals
EM 199511
ED Entered STN: 19951227
Last Updated on STN: 20000303
Entered Medline: 19951109

L10 ANSWER 10 OF 20 MEDLINE
AB Epithelioid cell granulomas identical to those of systemic sarcoidosis are occasionally observed within malignant neoplasms, particularly in the lymphatics draining a primary tumor. These histologic changes have been termed sarcoid reactions and are easily confused with systemic sarcoidosis. This report describes an extremely rare case of gastric **cancer** accompanied by sarcoid reactions in the regional lymph nodes and liver parenchyma near a tumor **metastasis**. A 63-year-old woman with advanced gastric **cancer** was **treated** by subtotal gastrectomy with dissection of the regional

lymph nodes and local excision of the liver tissue involved by **metastasis**. Microscopic examination of the resected lymph nodes and liver disclosed the presence of sarcoid-like granulomas. The absence of any clinical manifestations and the negative results of the Kveim test, chest radiograph, and laboratory tests, including that for the serum **angiotensin** converting enzyme excluded the possibility of systemic sarcoidosis. The presence of a sarcoid reaction in the liver parenchyma adjacent to a **metastasis** has never been reported previously.

AN 94034048 MEDLINE
DN 94034048 PubMed ID: 8219615
TI A case report of gastric cancer associated with sarcoid reactions in the regional lymph nodes and liver.
AU Hirota T; Kaneda M; Iwasa M; Tamaki H
CS Department of Surgery, Mie Prefectural Hospital of Shima, Mie, Japan.
SO SURGERY TODAY, (1993) 23 (9) 810-5.
Journal code: BFY; 9204360. ISSN: 0941-1291.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199312
ED Entered STN: 19940117
Last Updated on STN: 19940117
Entered Medline: 19931217

L10 ANSWER 11 OF 20 MEDLINE
AB A preferable route for administration of anti-**cancer** drugs together with **angiotensin**-II (AT-II) was examined by measuring the tissue concentration of drugs in resected specimens. Twenty five patients with gastric **cancer** were randomly divided into five groups, and 5-FU (250 mg) was given with or without AT-II intraoperatively. Group A; i.v. 5-FU alone (n = 5), Group B; i.v. 5-FU with AT-II (n = 5), Group C; i.a. 5-FU alone (n = 5), Group D; i.a. 5-FU with i.v. AT-II (n = 5) and Group E; i.a. 5-FU with AT-II (n = 5). 5-FU level in regional lymph nodes was statistically higher in Group D compared to other groups, while in tumor tissues it was markedly higher in Group E. The ratio of 5-FU level in tumor tissues to normal tissues (T/N) was higher in Groups D and E. In patients with advanced malignancies, response rates were 17% in i.v. anti-**cancer** drugs with AT-II group, 41% in i.a. anti-**cancer** drugs with i.v. AT-II group and 24% in i.a. anti-**cancer** drugs with AT-II group. Median survival time for each group were 6.3 months, 9.6 months and 14.2 months, respectively. It is concluded that intra-arterial infusion chemotherapy together with AT-II can be an effective **treatment** for advanced malignancies.

AN 91360033 MEDLINE
DN 91360033 PubMed ID: 1886590
TI 5-FU concentration in the tissue of gastric **cancer**, and evaluation of **cancer** chemotherapy with **angiotensin**-II.
AU Takahashi N
CS Department of Surgery, National Sendai Hospital, Japan.
SO NIPPON GEKA GAKKAI ZASSHI. JOURNAL OF JAPAN SURGICAL SOCIETY, (1991 Jul) 92 (7) 775-84.
Journal code: NGG; 0405405. ISSN: 0301-4894.
CY Japan
DT (CLINICAL TRIAL)

Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LA Japanese
FS Priority Journals
EM 199110
ED Entered STN: 19911027
Last Updated on STN: 19950206
Entered Medline: 19911004

L10 ANSWER 12 OF 20 MEDLINE
AB We used **treatment** with intra-arterial injection in cases of liver and peritoneal **metastasis** in progressive or recurrent gastric **cancer** patients. The investigation of the relationship between efficiency of therapy and survival period was evaluated. The effective rate of sequential **treatment** of peritoneal **metastasis** with MTX.5-FU in 34 cases was 35.3%, while that of liver **metastasis** with MMC combined with DSM in 12 cases was 50%. Although the effective rate among 16 cases **treated** with MMC.5-FU combined with **Angiotensin** II was 50%, no effect was recognized in the groups **treated** with AF and MF. In cases of peritoneal **metastasis** with MTX.5-FU, the prognosis PR cases was significantly better than that of NC.PD. For **treatment** of liver **metastasis** with MMC combined with DSM and MMC.5-FU combined with **Angiotensin** II, the PR prognosis was unsatisfactory and the survival period did not significantly improve compared with that of NC.PD.
In future cases of liver **metastasis**, these results indicate the extreme difficulty in maintaining therapy and controlling the lesion after PR. We speculated that sequential **treatment** of peritoneal **metastasis** with MTX.5-FU was useful because it significantly extended the survival period in PR cases.
AN 90358570 MEDLINE
DN 90358570 PubMed ID: 2117898
TI Evaluation of the liver and peritoneal **metastasis** in the **treatment** of gastric carcinoma with intra-arterial injection in terms of survival period.
AU Kitamura M; Arai K; Miyashita K
CS Dept. of Surgery, Tokyo Metropolitan Komagome Hospital.
SO GAN TO KAGAKU RYOHO [JAPANESE JOURNAL OF CANCER AND CHEMOTHERAPY], (1990 Aug) 17 (8 Pt 2) 1657-60.
Journal code: 6T8; 7810034. ISSN: 0385-0684.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
LA Japanese
FS Priority Journals
EM 199009
ED Entered STN: 19901026
Last Updated on STN: 20000303
Entered Medline: 19900926

L10 ANSWER 13 OF 20 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 2
AB The clinical efficacy and indications for **Angiotensin** II (AT II)-induced hypertension chemotherapy were evaluated as a drug delivery system in 101 patients with advanced carcinoma. The sites of primary tumor studied included stomach (44), pancreas (18), colon (16), esophagus (6), bile duct (4), liver (3), breast (7) and 3 other single organs. Seventy four cases had distant metastases (lymph node (25), liver (29), peritoneum

(16), and lung (4)). Additionally, the protocol was used 12 cases as postoperative adjuvant chemotherapy and 15 cases following exploratory laparotomy. The blood pressure was elevated to a level 1.5 times base-line. The regimens used consisted of MMC + ADR (55), FAM (38) and CDDP (8). The dosages administered were MMC 7 mg/m2, ADR 14 mg/m2 and 5-FU
350 mg/m2. The **cancer** chemotherapy protocol with AT II was repeated for an average of 2.6 cycles with a 2-3 week interval. The drug concentration in tumor tissues was increased 1.7 fold by AT II **treatment**. The response rate was 15.8% (CR 7 and PR 9), and in those patients with lymph node, liver and peritoneal metastases was 48.0, 6.9 and 6.3%, respectively. The serum levels of tumor markers decreased in
9 patients. Subjective symptoms, such as hoarseness, edema and pain, were improved. The mean survival in patients with distant **metastasis** who responded was 343 days, and in nonresponders was only 168 days ($p < 0.05$). The side effects of this therapy were slight, typically being grade
1 and 2. Thus, the chemotherapeutic agents studied in conjunction with AT II were effective in patients with lymph node **metastasis**. Additionally, this regimen could be performed safely with minimal side effects.

AN 1991:161374 BIOSIS
DN BA91:87174
TI CLINICAL EVALUATION OF CHEMOTHERAPY UNDER **ANGIOTENSIN** II-INDUCED HYPERTENSION IN PATIENTS WITH ADVANCED **CANCER**.
AU YAMAUE H; TANIMURA H; TERASHITA S; IWAHASHI M; TANI M; TSUNODA T; TAMAI M;
MORI K
CS DEP. GASTRONENTEROLOGICAL SURGERY, WAKAYAMA MED. COLL., 27-SHICHIBANCHO, WAKAYAMA 640, JPN.
SO ARCH JPN CHIR, (1990) 59 (4), 302-309.
CODEN: NIGHAE. ISSN: 0003-9152.
FS BA; OLD
LA English

L10 ANSWER 14 OF 20 MEDLINE
AB Fifty-five gastric **cancer** patients with liver **metastasis** received arterial infusion chemotherapy. In 14 patients who had lesions in
the liver intra-hepatic artery infusion chemotherapy was performed, while in 41 patients who had lesions in the liver and other sites intra-aortic infusion chemotherapy was performed. Methods for inserting the catheter into the aorta or hepatic artery and **treatment** schedules were reported previously. Between 1975 to 1981, 33 gastric **cancer** patients with liver **metastasis** were **treated** with 5-FU only (4 cases). MMC.5-FU (18 cases) and ADM.5-FU (11 cases). No response was seen, but minor response was seen in two cases. Between 1982 to 1988, 22 gastric **cancer** patients with liver **metastasis** were **treated** using arterial MMC.5-FU therapy combined with **angiotensin** II (13 cases), arterial MMC therapy combined with degradable starch microsphere (6 cases) and sequential MTX.5-FU (3 cases).
The response rate of MMC.5-FU therapy combined with **angiotensin** II was 5/13 (38%) including one complete response. The responders of MMC-combined DSM therapy were seen in 3 (50%) out of 6 patients. However, no response was seen in sequential MTX.5-FU therapy. In the present study,
a 61-year-old patient **treated** with MMC.5-FU combined with **angiotensin** II therapy, survived for 49 months after

treatment. In order to improve the prognosis of gastric **cancer** patients with liver **metastasis**, it is important to increase the delivery of anticancer drugs to the target tissues by using certain drugs like **angiotensin** II and DSM. In the future, further studies should be done to prolong the duration of remission by arterial chemotherapy.

AN 89391486 MEDLINE
DN 89391486 PubMed ID: 2506831
TI Arterial infusion chemotherapy in patients with gastric cancer in liver **metastasis** and long-term survival after **treatment**.
AU Kitamura M; Arai K; Miyashita K; Kosaki G
CS Dept. of Surgery, Tokyo Metropolitan Komagome Hospital.
SO GAN TO KAGAKU RYOHO [JAPANESE JOURNAL OF CANCER AND CHEMOTHERAPY], (1989 Aug) 16 (8 Pt 2) 2936-9.
Journal code: 6T8; 7810034. ISSN: 0385-0684.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
LA Japanese
FS Priority Journals
EM 198910
ED Entered STN: 19900309
Last Updated on STN: 20000303
Entered Medline: 19891023

L10 ANSWER 15 OF 20 MEDLINE
AB Over the past 6 years, we have **treated** 25 cases of pancreatic **cancer**, 6 cases of cholangioma in pancreas-head and 3 cases of **cancer** in duodenal papilla (2 cases Stage I, 5 cases stage II, 2 cases stage III, 25 cases stage IV). Twelve cases (10 unresectable cases, 1 hepatic **metastasis** case, 1 recurrent case) were **treated** with intra-arterial infusion chemotherapy using implantable Drug Delivery System, combined with **angiotensin**-II to increase the concentration of anti-**cancer** agents in **cancer** tissue. Twenty-four cases (70%) died in less than one year, so operation is not effective except for curative resection of cholangioma and duodenal papilla **cancer**. But exploratory laparotomy or inoperable cases given intermittent transcatheter arterial infusion chemotherapy (5-FU + ADM + MMC + **angiotensin**-II), showed favorable results (decrease of tumor size and pain in 2 cases; recanalization of obstruction in choledochus of 1 case). Especially trans-femoral or left subclavian arterial catheterization proved to be effective therapy for possibly giant or recurrent inoperable pancreatic **cancer** and hepatic **metastasis**. Using the drug delivery system, the technical approach to arterial infusion therapy and angiography has been readily undertaken. Quality of life has been improved, and course observation of the patient has been possible by imaging diagnosis and multidisciplinary **treatment** for advanced pancreatic **cancer**.

AN 89391439 MEDLINE
DN 89391439 PubMed ID: 2551218
TI Intra-arterial infusion chemotherapy in non-resectable pancreatic **cancer** using **angiotensin**-II and implantable drug delivery system.
AU Maruyama T; Koura Y; Kurisu Y; Kuroi K; Kai Y
CS Dept. of Surgery, Yoshida General Hospital, Hiroshima.
SO GAN TO KAGAKU RYOHO [JAPANESE JOURNAL OF CANCER AND CHEMOTHERAPY], (1989 Aug) 16 (8 Pt 2) 2735-9.
Journal code: 6T8; 7810034. ISSN: 0385-0684.
CY Japan

DT Journal; Article; (JOURNAL ARTICLE)
LA Japanese
FS Priority Journals
EM 198910
ED Entered STN: 19900309
Last Updated on STN: 19900309
Entered Medline: 19891023

L10 ANSWER 16 OF 20 MEDLINE
AB A study was made of the response rates of primary and metastatic lesions of advanced gastric **cancer** patients receiving chemotherapy from 1978 to 1987. The patients administered adriamycin (ADR), 5-FU, mitomycin C (MMC) or their analogues showed a response rate of 12.2% (5/41) in primary lesions, 15.9% (7/44) in liver metastases and 20.0% (4/20) in lymphnode metastases, respectively. The response rates were 14.3% (5/35) in primary lesions 16.7% (6/36) in liver metastases and 12.5% (2/16) in lymphnode metastases from chemotherapy using at least two kinds of the above drugs. No significant difference was seen among the response rates per above. By elevating blood pressure induced with **angiotensin** II, selective increase in blood flow in tumor tissue but no increase in normal tissue was observed experimentally (JNCI, 67, 663, 1981). This finding was clinically applied to **cancer** chemotherapy, termed Induced Hypertension Chemotherapy (IHC) for enhancing selective drug delivery to tumor tissue. The response rates were 47.6% (10/21) in primary lesions, 28.6% (2/7) in liver metastases and 81.8% (9/11) in lymphnode metastases when combination chemotherapy mainly with ADR, 5-FU and MMC with IHC was performed. Although the response rates were better than the results without IHC, the liver metastases did not indicate any statistical differences. The metastatic lesions in the lymphnode indicated a higher response than that of the primary lesions in the group **treated** with IHC, but no significant difference was seen. As to the primary lesions and the lymphnode metastases, the **treatment** with IHC showed higher response rates than those without IHC. It is conceivable that the results obtained would clinically prove the mechanism of selective drug delivery to tumor tissue as described in the experiment stated above. To detect the cause of unsatisfactory response rates of liver metastases, further clinical analysis of accumulated cases may be required.
AN 89271975 MEDLINE
DN 89271975 PubMed ID: 2499264
TI Chemotherapeutic effect on metastatic tumors.
AU Takahashi H; Sato H
CS Dept. of Clinical Cancer Chemotherapy, Tohoku University.
SO GAN TO KAGAKU RYOHO [JAPANESE JOURNAL OF CANCER AND CHEMOTHERAPY], (1989 Apr) 16 (4 Pt 2-1) 1255-9.
Journal code: 6T8; 7810034. ISSN: 0385-0684.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
LA Japanese
FS Priority Journals
EM 198906
ED Entered STN: 19900309
Last Updated on STN: 20000303
Entered Medline: 19890626

L10 ANSWER 17 OF 20 BIOSIS COPYRIGHT 2001 BIOSIS
AB Serum ACE activity was examined in cases of diseases of the thyroid gland.

The enzyme activity was compared with the concentration of total serum thyroxine (TT4) and total serum triiodothyronine (TT3). For this purpose the medical data of a group of healthy test persons (85 - and 85 .tau.) were contrasted with those of a group of 162 patients attending the out-patient department for thyroid gland diseases in our hospital (28 and 134 .tau., of whom 112 were aged between 21 and 60, and 50 above the age of 60). Among the patients there were 36 cases of euthyroid goiter, 59 of untreated and 36 of treated **hyperthyroidism**, 25 of hypothyroidism of varied genesis, and 6 patients suffering from as yet untreated thyroid cancer. We observed significant differences in ACE activity in the different groups. In cases of disorder of the thyroid gland there was a positive correlation between enzyme activity and hormone data. Where other causes which may influence its activity can be excluded, ACE reflects the effect of the hormones of the thyroid gland on the tissue. We kept under observation 15 patients suffering from thyroid cancer altogether, of whom 6 had no previous treatment, **whereas** in 9 thyroidectomy had been carried out, followed by radioactive iodine therapy. Irrespective of the timing of the examination, there was a significant increase in serum ACE activity (on average 365 U/l, as against 282 U/l, p < 0.01), if metastasis **had** occurred.

AN 1988:416775 BIOSIS
DN BA86:79387
TI THE BEHAVIOR OF ACE IN DISEASES OF THE THYROID GLAND.
AU MAYR K; STOCKHAMMER M
CS KROATENGASSE 2, A-4020 LINZ.
SO WIEN KLIN WOCHENSCHR, (1988) 100 (7), 203-208.
CODEN: WKWOAO. ISSN: 0043-5325.
FS BA; OLD
LA German

L10 ANSWER 18 OF 20 MEDLINE
AB The effect of **treatment** with intravenously administered **Angiotensin** II (AT II) on blood flow in normal and malignant tissues was investigated clinically. The time course of the effect of AT II was directly recorded by laser doppler velocimetry (LDV) via a probe placed on the surface of normal and malignant tissues. Intravenous administration of AT II resulted in an approximate 3.5 (1.3-14.0)-fold increase in blood flow in eleven malignant tissues, such as breast **cancer** with direct extension to the skin and abdominal skin **metastasis** of gastric adenocarcinoma. On the other hand, the blood flow in normal skin was decreased under AT II-induced hypertension, but a reactive hyperemia-like increase was observed soon after the withdrawal of AT II. These results strongly suggested that intravenously administered AT II can act as an adjuvant to enhance, by varying degrees, drug delivery to tumor tissue in **cancer** chemotherapy and that the administration of chemotherapeutic agents is undesirable soon after the withdrawal of AT II.

AN 86294553 MEDLINE
DN 86294553 PubMed ID: 2943227
TI Continuous measurement of tumor blood flow under hypertension induced by angiotensin II--clinical studies with laser Doppler velocimetry.
AU Kudo T; Abo S; Itabashi T; Watanabe K; Onodera K; Shimoma N; Kawamura Y; Hashimoto M; Kato T; Watanabe K; +

SO GAN TO KAGAKU RYOHO [JAPANESE JOURNAL OF CANCER AND CHEMOTHERAPY], (1986 Aug) 13 (8) 2549-54.
Journal code: 6T8; 7810034. ISSN: 0385-0684.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
LA Japanese
FS Priority Journals
EM 198609
ED Entered STN: 19900321
Last Updated on STN: 19900321
Entered Medline: 19860918

L10 ANSWER 19 OF 20 MEDLINE
AB We have developed a new method of intra-arterial infusion chemotherapy for non-resectable pancreatic **cancer**, in order to facilitate the selective delivery of a large amount of anticancer agent to the **cancer** lesion. This method was carried out as follows: (1) retrograde cannulation was performed by inserting a catheter into the splenic artery after splenectomy, and many of its branches were dissected out around the body and tail of the pancreas: (2) anticancer drugs (Adriamycin and Methotrexate) were infused together with **Angiotensin**-II to decrease the blood flow to non-malignant tissue and to increase the flow to **cancer** tissue. (3) Twenty-four to 48 hours after Methotrexate was infused, rescue was performed with an infusion of Prostaglandin-E1 to reduce the degree of cytotoxic damage to normal tissue. By using these methods, it was ascertained that a large quantity of the drugs had accumulated in the **cancer** tissue, even though its original blood flow had been established as very poor by radioisotope and angiographical examination. This therapy was useful not only for anticancer effects on the primary lesion but also the **prevention** of liver **metastasis**. Moreover, Methotrexate and rescue therapy were shown to have no remarkable side effects.
AN 85120947 MEDLINE
DN 85120947 PubMed ID: 4038597
TI Intra-arterial infusion chemotherapy for non-resectable pancreatic **cancer** using **angiotensin**-II and prostaglandin-E1.
AU Ishikawa O; Ohhigashi H; Iwanaga T
SO GAN TO KAGAKU RYOHO [JAPANESE JOURNAL OF CANCER AND CHEMOTHERAPY], (1985 Feb) 12 (2) 235-44.
Journal code: 6T8; 7810034. ISSN: 0385-0684.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
LA Japanese
FS Priority Journals
EM 198503
ED Entered STN: 19900320
Last Updated on STN: 19900320
Entered Medline: 19850320

L10 ANSWER 20 OF 20 MEDLINE
AB The response of **cancer** to various anticancer drugs is tumor-size dependent in many aspects. In general, problems stem partly from the fact that the entire tumor cell populations do not respond equally to a certain **treatment**. As a result of recent progress in **cancer** biology, it has become evident that cellular heterogeneity of the tumor underlies the difficulties of **treating** primary and metastatic tumors with chemotherapy. Moreover, as tumors grow, marked diversity develops on the tissue level as well. An uneven distribution with an

increase of areas of lower growth fraction and of poorer drug delivery is more distinct in larger tumors. Heterogeneous distribution and low levels of tumor blood flow are considered to be causally related to the heterogeneous nature of tumor tissue. Considering the lack of evidence of a lymphatic system within the tumor, increased interstitial fluid pressure may be a natural result that further impedes blood flow in the tumor. The fact that the temporary and selective increase in tumor tissue blood flow by **angiotensin**-induced hypertension produces a remarkable chemotherapeutic effect should vividly indicate that delivery of the drug to the tumor is really the 'bottleneck' of **cancer** chemotherapy. Tumor-size-related change in the transvascular and extravascular transport of molecules and its relevance to chemotherapy are also discussed in this article.

AN 85201447 MEDLINE
DN 85201447 PubMed ID: 3888381
TI Some aspects of size-dependent differential drug response in primary and metastatic tumors.
AU Abe I; Suzuki M; Hori K; Saito S; Sato H
SO CANCER AND METASTASIS REVIEWS, (1985) 4 (1) 27-39. Ref: 148
Journal code: C9H; 8605731. ISSN: 0891-9992.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA English
FS Priority Journals
EM 198507
ED Entered STN: 19900320
Last Updated on STN: 19900320
Entered Medline: 19850709